

Diabetic Nephropathy (DN)

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Diabetes has two major vascular complication:

1. MORTALITY is related to MACROVASCULAR complications ,affect large blood vessels like:

- CAD.
- Stroke.
- PVD, the mechanism is variable : ischemia , arthrosclerosis , hypertension.

★ These complications have no relation to diabetic nephropathy.

2. MORBIDITY is related to MICROVASCULAR complications ,affect small blood vessels like:

- EYE :in retinal artery, called "diabetic retinopathy".
- KIDNEY : called "diabetic nephropathy".
- NERVE :in peripheral nerves, called "diabetic neuropathy".

Diabetic Nephropathy:

A microvascular complication of diabetes marked by albuminuria and a deteriorating course from normal renal function to ESRD.

- NB**
- ▶ The disease start by microalbuminuria, then progress slowly to nephrotic syndrome (proteinuria), then progress to End Stage Renal Disease. (It is very progressive disease)
 - ▶ In study in KKHU nephro clinic found that more than 46% of chronic kidney disease are having diabetes.

Causes of Chronic Renal Failure: (in KKHU)

- | | |
|--|--------|
| - Diabetic mellitus. | 46.43% |
| - Glomerulonephritis. | 22.32% |
| - Hypertension. | 15.18% |
| - Ischemic cardiac failure and cardiomyopathy. | 6.25% |
| - Unknown Causes. | 4.46% |
| - Miscellaneous Cause. | |

- NB**
- ▶ Diabetes is the commonest cause to ESRD (or renal failure).
 - ▶ About 50% of patient in dialysis are due to diabetes. (international number)





Study

In KSA :

- ▶ Hemodialysis patients : 10,000 to 20,000 patients.
- ▶ 20% to 35% of them is due to diabetes. (It is a common cause that bring the patient to dialysis)
- ▶ We have less number of patients reaching dialysis because patient usually die before reaching ESRD.
- ▶ Cost of care in dialysis = 205,920,000 SR

NB:

- ▶ Patients without diabetes has a mortality rate of 7% per year, while **diabetic patients** have a mortality rate of **14.6% per year** and if they have chronic kidney disease the mortality is 24% and only a little of them go to dialysis because they die before reaching to ESRD due to other cause like CAD or stroke.
- ▶ So, diabetes is a very aggressive disease in both morbidity and mortality and a main cause of ESRD.
- ▶ 5 year survival is poor & more with diabetic patients.
- ▶ The 5 year survival of dialysis non diabetic patients is about 80% while in diabetic patients it is about 20%.
- ▶ Mortality rate is very high more than colonic cancer patients! (50-60% will be alive after 5 years while in diabetes it is 20%)
- ▶ In a study in KKHU in diabetic pts in nephrology clinic looking for other complication of diabetes showed that pts with high cholesterol are 51%, hypertension are 96.7%, ischemic heart disease about 60%, retinopathy 47%, 56% have PVD. (that mean when the pts reach the stage of dialysis he will have other complications)

Complication of diabetic nephropathy patients at KKHU:

- | | |
|-----------------------------|-------------------------|
| - Diabetic foot. | - Elevated cholesterol. |
| - Uncontrolled blood sugar. | - Hypertension. |
| - Death. | - CAD. |
| - Amputation. | - Neuropathy. |
| - ESRD. | - Retinopathy. |
| - Blindness. | - PVD. |



PREVALENCE:

- **Insulin dependent diabetes mellitus: (Type 1)**

- Usually diabetic nephropathy, starts after 5 - 10 years.
- 30 - 50% after 20 years .
- Male preponderance 1.7 : 1
- Nephrotic syndrome occur in 10 - 40%
- GFR fall by 1 - 12 ml/min/year
- Nephrotic proteinuria has poor renal outcome.
- Diabetic retinopathy occur in 90% .

- If you have type 1 diabetes without retinopathy it is very unusual.

(كما قال الدكتور أشك أن عنده diabetes)

- **Non-Insulin dependent diabetes mellitus: (Type2)**

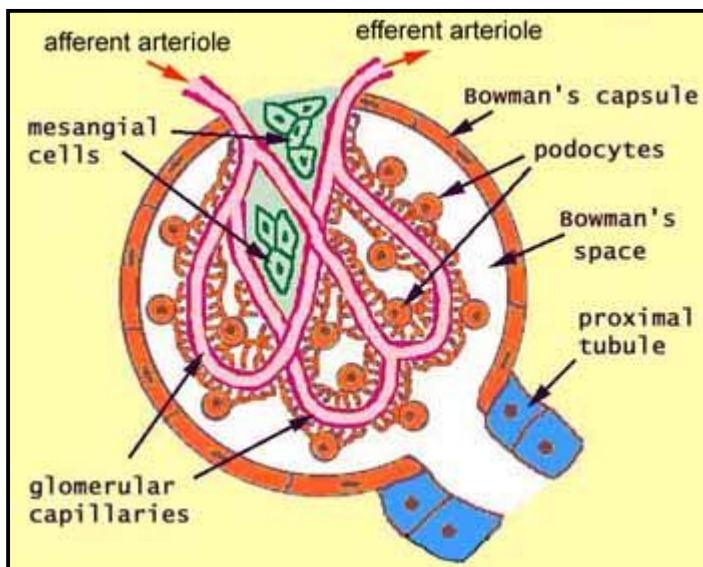
- Prevalence of proteinuria "diabetic nephropathy" is 6 - 50%.
- Variable racial and genetic factors:
 - High prevalence of diabetic nephropathy in pima Indian, black, and Arabs.
- Increased prevalence of diabetic nephropathy with duration.
- Mortality of diabetic renal failure is 2.5 time higher than non-diabetics
- 30% of ESRD is diabetic

Study of 125 patients in KKHU:



Study

- Duration of DM 9.46 years.
- Nephrotic syndrome 5.6%
- Microalbuminuria 16.8%
- Retinopathy 37%
- **In conclusion:** 35% will develop diabetic nephropathy.
- Clinical proteinuria 30.4%
- Hypertension 36.8%



[For the figure]

In the glomeruli, there is afferent and efferent arterioles, the blood come from the afferent and go out from the efferent, the afferent arteriole get branched to several capillaries about 10-13 capillaries lined with endothelial cells beneath it is the basement membrane and beneath the basement membrane is the epithelial cells like (أخطبوط) that have foot processes , this is the glomerulus

Pathogenesis (what happened in diabetes):

- Increased intraglomerular pressure:
 - Hyperglycemia shift a lot of water from the intracellular to intravascular and the pressure will increase.
- Mesangial cell expansion:
 - Because of increased pressure and the blood speed lead to increased oxygen radicals and reactive oxygen species leading to stimulate the release of many factors that increase its growth.
- Reactive Oxygen Species (ROS).
- Endothelial cell dysfunction:
 - Also happen due to increased pressure.
- Increased Glomerular Basement Membrane Thickness and Interstitial Fibrosis:
 - The basement membrane is renewed but in some diabetic pts this endothelial cells get swollen and enlarged and then cast so there will be no basement membrane.

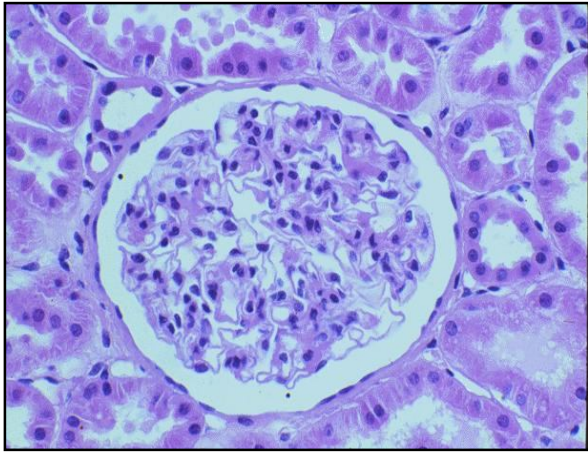
- NB**
- ▶ When mesangial cell expanded it going to increase the extracellular matrix then forming the glomerular sclerosis either diffuse or nodular.
 - ▶ The latter called (Kimmelstiel- Wilson) which is characteristic for diabetic nephropathy.

How do complications occur?

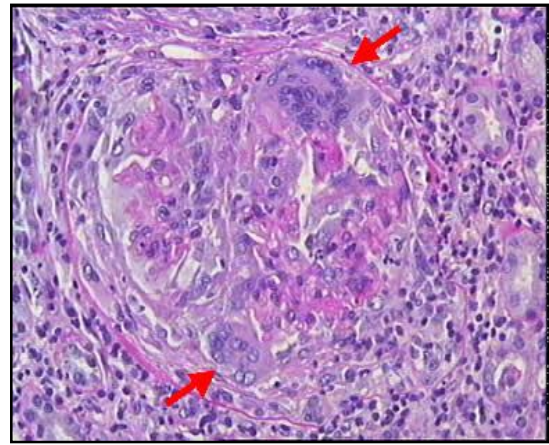
(due to increased intracapillary pressure and also other factors)

- Activation of Polyol Pathway.
- Accumulation of Advanced Glycosylation End Products.
 - > Glycosylation of the protein changes the protein.
- Protein Kinase C Pathway.
- Flux Through the Hexosamine Pathway.
- Oxygen Radicals and Enhanced Oxidative Stress.
- Altered Expression of Growth Factors and Vasoactive Mediators
 - > If you take a blood sample from diabetic pts you will find a lot of growth factors.





NORMAL



Glomerular Sclerosis

Risk Factors for Diabetic Nephropathy:

- Family History of Hypertension or Kidney Disease or Diabetic Nephropathy.
- Smoking.
- Hypertension.
- Dyslipidemia.
- Decreased Kidney Function (Renal Impairment).
- Poorly controlled diabetes with $Hb_{A1C} > 8.5\%$.
- Duration of Diabetes:
 - Type 1: > 10 years.
 - Type 2: > 5 years.
- Microalbuminuria or proteinuria.

Epidemiology of diabetic nephropathy : Genes?

(If pt with diabetes has a relative with type 2 diabetes and in renal dialysis)

- | | |
|---------------------------------------|---------------------------------------|
| - Relatives of Type II on dialysis: | x5 risk of ESRD |
| - If he has Both parents on dialysis: | 46% risk of diabetic nephropathy (DN) |
| - One with Proteinuria: | 23% risk of DN |
| - No DN of their family (parents): | 14% risk of DN |

- ★ This shows familial tendency.
- ★ Those are high risk people and they should have active aggressive management on diabetes.

Natural History of Diabetic Nephropathy (DN):

1. Increase BP.
2. Decrease GFR.
3. Increase cardiovascular death risk.

- NB**
- ▶ With damaged endothelial and detachment, there will be microalbuminuria and once macroalbuminuria happen, the pressure will start to be increased, the GFR start to decrease, mortality will increase, and the cardiovascular death rate will increase.
 - ▶ Proteinuria usually progress.
 - ▶ Development of macroalbuminuria heralds rapid decline in glomerular filtration in type II diabetes.
 - ▶ In Type II DM with Macroalbuminuria, \uparrow pressure \rightarrow \downarrow GFR. So, \uparrow CVS complication.
 - ▶ In pts with microalbuminuria there is no change in GFR but if pts get macroalbuminuria the GFR will start to decrease until reach the ESRD.

Clinical Course & Natural History:

(these stages takes long time until progress to ESRD and are more clear in type 1 diabetes)

• Stage 1:

- Renal Hypertrophy & Hyperfiltration
 - Increased capillary pressure makes the kidney function normal, but in other chronic kidney diseases, there is decrease in GFR and lead to fibrosis because of increased intraglomerular pressure.
 - In US the kidney appears normal or close to normal.
- Increase GFR [20 - 40%]
 - There will be increase in GFR in :
 - Type I DM : to about 50% [125 - >150 ml/min]
 - Type II DM: is up to 45% [117 - 133 ml/min]
 - It lasts around (takes about): 3-5 years.
- No microalbuminuria.

• Stage 2:

- Clinically silent stage.
- Lasting 5 - 15 years.
- Histology: Basement membrane thickening.
- No microalbuminuria.



- Stage 3:

- Incipient nephropathy.
- Microalbuminuria
 - First sign and the most important one.
 - There is 2 types of albuminuria according to the dipstick (regular type) if it positive that mean that it is macroalbuminuria more than 300mg/day or 200ug/min and if it is negative but the lab by special tests catch albumin but between:
 - 30 - 300 mg/day
 - 20 - 200 ug/min
 } we call it microalbuminurea.
 - If it less, it is normal.
- ACR: M- 2.5 F-3.5 mg/mmol
- Mild increase in BP
 - Loss of nocturnal dippers
- Falling GFR towards normal
 - When there is increase more in BP, the GFR will decrease , and when we control the BP we will discontinue the process.
- It is reversible stage.

- NB**
- ▶ Microalbuminuria present in small amount less than 300. So, dipstick test will not detect it.
 - ▶ We need special test e.g. immunoassay method or special dipstick to detect it.
 - ▶ This stage takes 10 years in type I DM and about 2-3 years in type II DM and that's why we need to screen them regularly.

- Stage 4:

- Overt Nephropathy
 - Means "macroalbuminuria" & can be detected by dipsticks
- Increasing proteinuria.
- GFR falls at about 10 ml/min/year.
 - Normally, it fall around 1 ml/min/year.
- Strong correlation with blood pressure.
 - BP will be high and hard to control.

- Stage 5:

- End stage renal disease (ESRD).



Stages of Diabetic Nephropathy :

• MICROALBUMINURIA:

- Normal albuminuria = "1.5 - 20 ug/min" OR "20 mg /24hrs"
- Microalbuminuria = "20- 200 ug/min" OR "30-300 mg /24hrs"
- Highly predictive of subsequent development nephropathy.
- 86 % with albuminuria will develop nephropathy vs 2.5 % without it.
- Microalbuminuria in type I is different than type II, because in type II it is associated with increased mortality with cardiovascular disease.
- We detect it with special type of dipstick or more recent and common test (albumin creatinine ratio).
- How to measure albumin /creatinine ratio:
 - ♦ Early morning sample. (first voided)
 - ♦ Short collection of urine with albuminuria to creatinine ratio.
 - ♦ Overnight collection, then send it to the lab.
- Check dipstick.
- 3 consequent measurement over 3 months.
- Can be positive in:
 - Uncontrolled DM
 - Uncontrolled BP
 - UTI
 - CHF
 - Smoking before the test.
 - Doing exercise before the test.
- It is associated with other abnormalities, that mentioned above, so we need to exclude it before beginning the treatment.

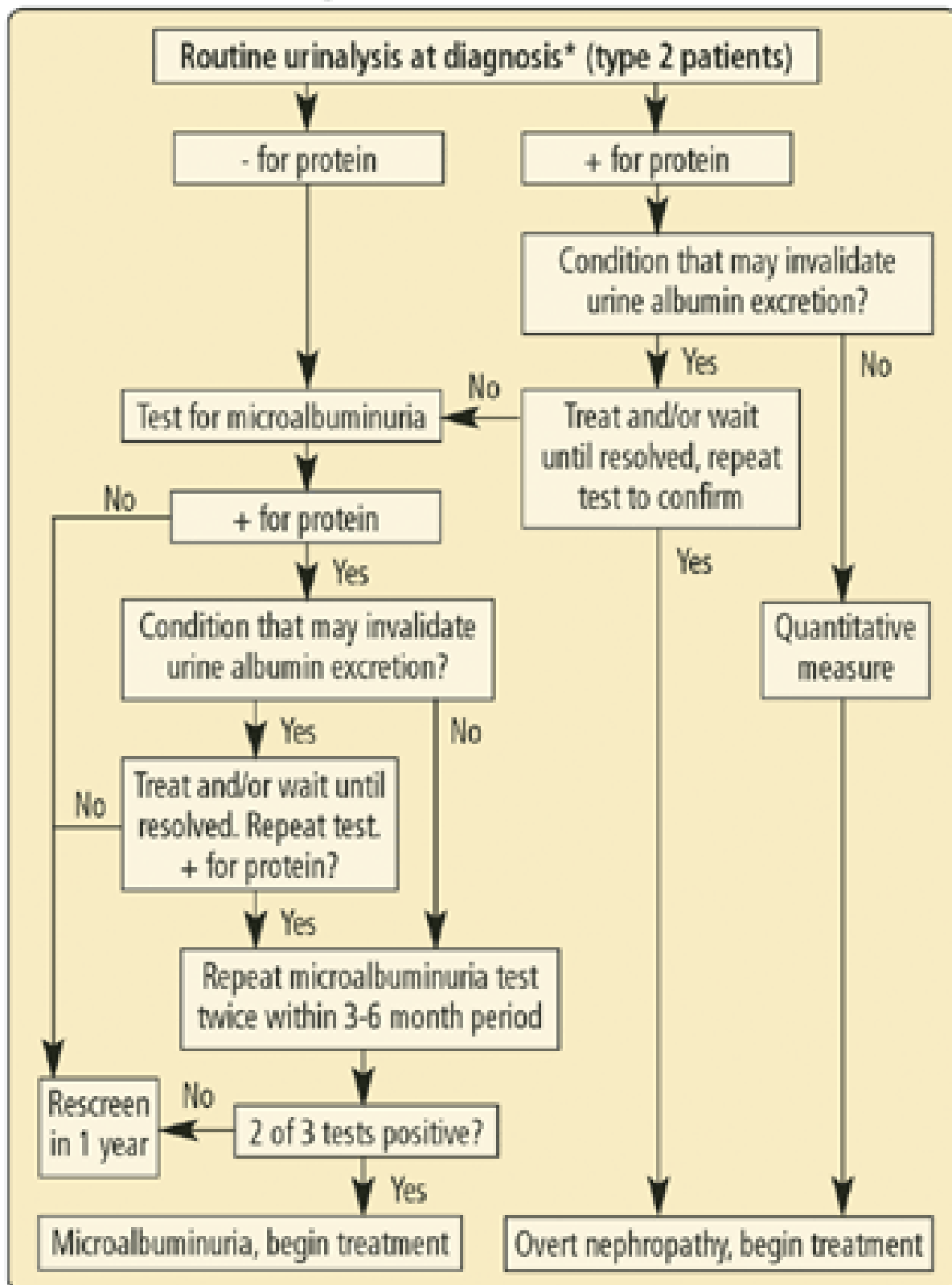
- NB**
- ▶ In DM type 1, 85% will develop microalbuminureia in early age. So, we wait 5 years after diagnosis to detect it.
 - ▶ But in type 2 once diagnosed we check for microalbuminuria & most of patients will have cardiovascular complications.
 - ▶ Albumin creatinin if 2.5-30 mg/mmol or albuminuria 25-300 mg /24hrs for male and 3.5-30 or 30-300 overnight albuminurea in female. (+ve protienuria)

• Screening of microalbuminuria:

- In type I, check after 5 years, then every year, but,
- In type II, check immediately and after that every month, because the pt may have DM for long time.
- If it is positive ask about the positives above and if one of them is present repeat it after one month, if it negative, it is good and if not then start to control because this is high risk pt and may get cardiovascular disease.
- Repeat it 3 times before label him as microalbuminurea pt.
- Don't delay the re-test more than 6 months.



FIGURE 1. Screening for Microalbuminuria



** In type 1 diabetes, screening for albuminuria should begin with puberty and after 5 years' disease duration.*

Prevention and Treatment of Diabetic Nephropathy:

- Glycemic control.

- The most important one, but need multiple medication & multiple injection.
- Treat BP aggressively.
- Aggressively treat proteinuria.
- Reduce albumin excretion Rate.
- ACE Inhibitors.
- A receptor II antagonists.
- Protein Restriction.
- Stop Smoking.
- Treat Hyperlipidemia.

International Studies Hyperglycemia :

The most important 2 are "DCCT" and "UKPDS"

- Meta-analysis (Wang)
- WESER
- DCCT. (Diabetes Complication Control Trial), for type I DM.
- Kumamoto.
- UKPDS. (United Kingdom Prospective Diabetes Study), for type II DM.

★ Overall, better control of DM lead to less complication including microproteinuria.

Important Point About Treatment :

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B

- ▶ Major complication of ACEi is hyperkalemia.
- ▶ We can add diuretics (thiazide) that can aggravate effect of ACEi causing lose of K⁺ & less retention of fluids.
- ▶ Aldactone (K⁺ sparing) may added causing less proteinuria & may decrease the fibrosis process in heart but until now not recommended.
- ▶ We combine drugs to lower the pressure more and to reduce the complication of ACE or ARB of hyperkalemia to combine it with diuretics(thiazide)which has 2 advantages lowering blood pressure and reduce the potassium(some little studies showed that spironolactone is for benefit although it is K sparing diuretics).
- ▶ Most Common Cause of Failing to Reduce Proteinuria with ACE Inhibitor or ARB is **High SALT intake (>5 grams/day)**

- Intensive Multi-risk Factor Intervention Improves Outcomes in Type 2 Diabetes:
 - According to this new study, lower glucose, lower hypertension, do exercise, lower the lipid and aspirin and stop smoking and they found that the complication all decrease, and we go with it when the pt is high risk pt.
- Protein Restriction:
 - The usual protein eating is 1.5 g/kg/day but we reduce it to reduce proteinuria to 0.8 g / kg/ day
- RENAAL Trial:
 - The pts with anemia has more incidence of ESRD and the correction may have a role.
- Most type of anemia is normocytic normochromic some time its iron deficiency anemia.

Management of Diabetic Nephropathy

Is it Reversible?

- One pt non diabetic with renal failure had kidney transplant of Diabetic pt and it was diseased. Then after while, it get normal in the non DM pt.
- They try it in animals and it succeeded.
- Diabetic nephropathy it is reversible after pancreas transplantation due to there is no diabetes anymore

Complication:

- Renal papillary necrosis:

- لم يتكلم عنها
- Occur in 5-65% of patient.
 - Affect both kidney in 65%.
 - More common in women.
 - Long standing disease.
 - Can be symptomatic or with renal colic.
 - Microscopic haematuria or pyuria.
 - Proteinuria is common.
 - Ring shadow or moth-eaten calyces.
 - Treatment.

- Autonomic neuropathy:
 - Occur in 40%.
 - Disappearance of nocturia.
 - Increase residual volume.
 - Incontinence.
 - Increase UTI.
 - Ultrasound scanning & uroflowmetry.
 - Regular voiding & intermittent catheterization.
 - Betanecol chloride.
- Urinary bacterial infection:
 - Bacteria is common in diabetic women.
 - Urinary tract is not common than control.
 - Can be asymptomatic.
 - UTI has severe complication.
 - Perinephric abscess.
 - Anaerobic gas forming organism.
- Has more perineal abscesses.
- Renal tubular acidosis:
 - Hypoglycemia.

Renal replacement therapy:

(considered when having ESRD)

- Transplantation.(Most Important)
- Hemodialysis.
- Peritoneal dialysis.

Take home message :

- DN is progressive kidney disease
- Characterized by hypertension & proteinuria & progressive loss of kidney function
- Most common cause to ESRD
- More likely to die rather than progress to ESRD
- Multirisk factor intervention is critical
- Lowering BP with RAAS blockade is critical
- Prevent cardiovascular morbidity & mortality
- Lowering BP <130/80 mmHg
- Reducing proteinuria
- Inhibition of rennin angiotensin system
- Multiple risk factor intervention: glycemia, dyslipidemia, physical activity, aspirin, smoking cessation.

Diabetic Nephropathy Management :

| Parameter | Target |
|------------------------|---------------------------------------|
| Lower BP | <130/80 mmHg |
| Block RAAS | ACEi or ARB to max tolerated |
| Improve glycemia | HbA1c <6.5 % (insulin / TZD) |
| Lower LDL cholesterol | <100 (70) mg /dl (statin + other) |
| Anemia management | Hb 11-12 g/dl (Erythropoietin + Iron) |
| Endothelial protection | aspirin |
| Smoking | cessation |

∴ The End ∴

Done By : Nephro Team

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